General

Guideline Title

Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care.

Bibliographic Source(s)

National Clinical Guideline Centre. Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 59 p. (Clinical guideline; no. 182).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Chronic Conditions. Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Sep. 36 p. (Clinical guideline; no. 73).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked as [2008], [2008, amended 2014], [2014] or [new 2014]:

- [2008] indicates that the evidence has not been reviewed since 2008
- [2008, amended 2014] indicates that the evidence has not been reviewed since 2008, but changes have been made to the recommendation wording that change the meaning
- [2014] indicates that the evidence has been reviewed but no change has been made to the recommended action
- [new 2014] indicates that the evidence has been reviewed and the recommendation has been updated or added.

The wording used in the recommendations in this guideline (for example words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendation) and is defined at the end of the "Major Recommendations" field.

Investigations for Chronic Kidney Disease (CKD)

Measuring Kidney Function

Creatinine-based Estimate of Glomerular Filtration Rate (eGFRcreatinine)

Whenever a request for serum creatinine measurement is made, clinical laboratories should report an estimate of glomerular filtration rate (eGFR) using a prediction equation in addition to reporting the serum creatinine result*. [2014]

Clinical laboratories should:

- Use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to estimate GFRcreatinine, using creatinine assays with calibration traceable to standardised reference material.
- Use creatinine assays that are specific (for example, enzymatic assays) and zero-biased compared with isotope dilution mass spectrometry (IDMS).
- Participate in a United Kingdom (UK) national external quality assessment scheme for creatinine. [new 2014]

Apply a correction factor to GFR values estimated using the CKD-EPI creatinine equation for people of African-Caribbean or African family origin (multiply eGFR by 1.159). [new 2014]

In people with extremes of muscle mass – for example, in bodybuilders, people who have had an amputation or people with muscle wasting disorders – interpret eGFRcreatinine with caution. (Reduced muscle mass will lead to overestimation and increased muscle mass to underestimation of the GFR.) [2008]

Advise people not to eat any meat in the 12 hours before having a blood test for eGFRcreatinine. Avoid delaying the despatch of blood samples to ensure that they are received and processed by the laboratory within 12 hours of venepuncture. [2008]

*eGFRcreatinine may be less reliable in certain situations (for example, acute kidney injury, pregnancy, oedematous states, muscle wasting disorders, and in people who are malnourished or have had an amputation) and has not been well validated in certain ethnic groups (for example, in people of Asian family origin).

Cystatin C-based Estimate of GFR (eGFRcystatinC)

Whenever a request for serum cystatin C measurement is made, clinical laboratories should report an estimate of glomerular filtration rate (eGFRcystatinC) using a prediction equation (see the following recommendation) in addition to reporting the serum cystatin C result. [new 2014]

When an improved assessment of risk is needed (see "When to Use a Cystatin C-based Estimate of GFR for Diagnosis of CKD," below), clinical laboratories should use the CKD-EPI cystatin C equation to estimate GFRcystatinC. [new 2014]

Clinical laboratories should use cystatin C assays calibrated to the international standard to measure serum cystatin C for cystatin C-based estimates of GFR. [new 2014]

Interpret eGFRcystatinC with caution in people with uncontrolled thyroid disease because eGFRcystatinC values may be falsely elevated in people with hypothyroidism and reduced in people with hyperthyroidism. [new 2014]

Reporting and Interpreting GFR Values

Clinical laboratories should report GFR either as a whole number if it is 90 ml/min/1.73 m^2 or less, or as 'greater than 90 ml/min/1.73 m^2'. [new 2014]

If GFR is greater than 90 ml/min/1.73 m^2, use an increase in serum creatinine concentration of more than 20% to infer significant reduction in kidney function. [new 2014]

Interpret eGFR values of 60 ml/min/1.73 m^2 or more with caution, bearing in mind that estimates of GFR become less accurate as the true GFR increases. [2014]

Confirm an eGFR result of less than 60 ml/min/1.73 m^2 in a person not previously tested by repeating the test within 2 weeks. Allow for biological and analytical variability of serum creatinine (±5%) when interpreting changes in eGFR. [2008]

When to Use a Cystatin C-based Estimate of GFR for Diagnosis of CKD

Consider using eGFRcystatinC at initial diagnosis to confirm or rule out CKD in people with:

- An eGFR creatinine of 45–59 ml/min/1.73 m^2, sustained for at least 90 days and
- No proteinuria (albumin:creatinine ratio [ACR] less than 3 mg/mmol) or other marker of kidney disease. [new 2014]

Do not diagnose CKD in people with:

- An eGFR creatinine of 45–59 ml/min/1.73 m^2 and
- An eGFRcystatinC of more than 60 ml/min/1.73 m^2 and
- No other marker of kidney disease. [new 2014]

When Highly Accurate Measures of GFR Are Required

Where a highly accurate measure of GFR is required – for example, during monitoring of chemotherapy and in the evaluation of renal function in potential living donors – consider a reference standard measure (inulin, ^{51}Cr-EDTA, ^{125}I-iothalamate or iohexol). [2008]

Proteinuria

Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. [2008]

To detect and identify proteinuria, use urine ACR in preference to protein:creatinine ratio (PCR), because it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of high levels of proteinuria (ACR 70 mg/mmol or more), PCR can be used as an alternative. ACR is the recommended method for people with diabetes. [2008, amended 2014]

For the initial detection of proteinuria, if the ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested. [2008, amended 2014]

Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. [2008, amended 2014]

Quantify urinary albumin or urinary protein loss as in the recommendation above for:

- People with diabetes
- People without diabetes with a GFR of less than 60 ml/min/1.73 m^2. [2008, amended 2014]

Quantify by laboratory testing the urinary albumin or urinary protein loss of people with a GFR of 60 ml/min/1.73 m^2 or more if there is a strong suspicion of CKD (see also "Who Should Be Tested for CKD," below). [2008]

Haematuria

When testing for the presence of haematuria, use reagent strips rather than urine microscopy.

- Evaluate further if there is a result of 1+ or more.
- Do not use urine microscopy to confirm a positive result. [2008]

Managing Isolated Invisible Haematuria

When there is the need to differentiate persistent invisible haematuria in the absence of proteinuria from transient haematuria, regard 2 out of 3 positive reagent strip tests as confirmation of persistent invisible haematuria. [2008]

Persistent invisible haematuria, with or without proteinuria, should prompt investigation for urinary tract malignancy in appropriate age groups. [2008]

Persistent invisible haematuria in the absence of proteinuria should be followed up annually with repeat testing for haematuria (see above recommendations), proteinuria or albuminuria, GFR and blood pressure monitoring as long as the haematuria persists. [2008]

Who Should Be Tested for CKD

Monitor GFR at least annually in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors (for example, cyclosporin or tacrolimus), lithium and non-steroidal anti-inflammatory drugs (NSAIDs). [2008, amended 2014]

Offer testing for CKD using eGFRcreatinine and ACR to people with any of the following risk factors:

- Diabetes
- Hypertension
- Acute kidney injury (see recommendation under "Acute Kidney Injury and CKD" below)
- Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- Structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- Multisystem diseases with potential kidney involvement – for example, systemic lupus erythematosus
- Family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease
- Opportunistic detection of haematuria. [new 2014]

Do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD. [2008, amended 2014]

Classification of Chronic Kidney Disease

Classify CKD using a combination of GFR and ACR categories (as described in table 1 in the original guideline document). Be aware that:

- Increased ACR is associated with increased risk of adverse outcomes.
- Decreased GFR is associated with increased risk of adverse outcomes.
- Increased ACR and decreased GFR in combination multiply the risk of adverse outcomes. [new 2014]

Do not determine management of CKD solely by age. [new 2014]

Investigating the Cause of CKD and Determining the Risk of Adverse Outcomes

Agree a plan to establish the cause of CKD during an informed discussion with the person with CKD, particularly if the cause may be treatable (for example, urinary tract obstruction, nephrotoxic drugs or glomerular disease). [new 2014]

Use the person's GFR and ACR categories (see table 1 in the original guideline document) to indicate their risk of adverse outcomes (for example, CKD progression, acute kidney injury, all-cause mortality and cardiovascular events) and discuss this with them. [new 2014]

Indications for Renal Ultrasound

Offer a renal ultrasound scan to all people with CKD who:

- Have accelerated progression of CKD (see "Defining Progression," below)
- Have visible or persistent invisible haematuria
- Have symptoms of urinary tract obstruction
- Have a family history of polycystic kidney disease and are aged over 20 years
- Have a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5)
- Are considered by a nephrologist to require a renal biopsy. [2008, amended 2014]

Advise people with a family history of inherited kidney disease about the implications of an abnormal result before a renal ultrasound scan is arranged for them. [2008]

Frequency of Monitoring

Agree the frequency of monitoring (eGFRcreatinine and ACR) with the person with, or at risk of, CKD; bear in mind that CKD is not progressive in many people. [new 2014]

Use table 2 in the original guideline document to guide the frequency of GFR monitoring for people with, or at risk of, CKD, but tailor it to the person according to:

- The underlying cause of CKD
- Past patterns of eGFR and ACR (but be aware that CKD progression is often nonlinear)
- Comorbidities, especially heart failure
- Changes to their treatment (such as renin–angiotensin–aldosterone system [RAAS] antagonists, NSAIDs and diuretics)
- Intercurrent illness
- Whether they have chosen conservative management of CKD. [new 2014]

Defining Progression

Define accelerated progression of CKD as:

- A sustained decrease in GFR of 25% or more and a change in GFR category within 12 months or
- A sustained decrease in GFR of 15 ml/min/1.73 m^2 per year. [new 2014]

Take the following steps to identify the rate of progression of CKD:

- Obtain a minimum of 3 GFR estimations over a period of not less than 90 days.
- In people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR – for example, acute kidney injury or starting renin–angiotensin system antagonist therapy. [2008, amended 2014]

Be aware that people with CKD are at increased risk of progression to end-stage kidney disease if they have either of the following:

- A sustained decrease in GFR of 25% or more over 12 months or
- A sustained decrease in GFR of 15 ml/min/1.73 m^2 or more over 12 months. [2008, amended 2014]

When assessing CKD progression, extrapolate the current rate of decline of GFR and take this into account when planning intervention strategies, particularly if it suggests that the person might need renal replacement therapy in their lifetime. [2008, amended 2014]

Risk Factors Associated with CKD Progression

Work with people who have any of the following risk factors for CKD progression to optimise their health:

- Cardiovascular disease
- Proteinuria
- Acute kidney injury
- Hypertension
- Diabetes
- Smoking
- African, African-Caribbean or Asian family origin
- Chronic use of NSAIDs
- Untreated urinary outflow tract obstruction. [new 2014]

In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression. [2008]

Acute Kidney Injury and CKD

Monitor people for the development or progression of CKD for at least 2–3 years after acute kidney injury, even if serum creatinine has returned to baseline. [new 2014]

Advise people who have had acute kidney injury that they are at increased risk of CKD developing or progressing. [new 2014]

Information and Education

Offer people with CKD education and information tailored to the severity and cause of CKD, the associated complications and the risk of progression. [2008]

When developing information or education programmes, involve people with CKD in their development from the outset. The following topics are suggested.

- What is CKD and how does it affect people?
- What questions should people ask about their kidneys?
- What treatments are available for CKD, what are their advantages and disadvantages and what complications or side effects may occur as a result of treatment/medication?
- What can people do to manage and influence their own condition?
- In what ways could CKD and its treatment affect people's daily life, social activities, work opportunities and financial situation, including benefits and allowances available?
- How can people cope with and adjust to CKD and what sources of psychological support are available?

- When appropriate, offer information about renal replacement therapy (such as the frequency and length of time of dialysis treatment sessions or exchanges and preemptive transplantation) and the preparation required (such as having a fistula or peritoneal catheter).
- Conservative management and when it may be considered. [2008]

Offer people with CKD high-quality information or education programmes as appropriate to the severity of their condition to allow time for them to fully understand and make informed choices about their treatment. [2008]

Healthcare professionals providing information and education programmes should ensure they have specialist knowledge about CKD and the necessary skills to facilitate learning. [2008]

Healthcare professionals working with people with CKD should take account of the psychological aspects of coping with the condition and offer access to appropriate support – for example, support groups, counselling or a specialist nurse. [2008]

Lifestyle Advice

Encourage people with CKD to take exercise, achieve a healthy weight and stop smoking. [2008]

Dietary Interventions

Offer dietary advice about potassium, phosphate, calorie and salt intake appropriate to the severity of CKD. [2008, amended 2014]

Where dietary intervention is agreed this should occur within the context of education, detailed dietary assessment and supervision to ensure malnutrition is prevented. [2008]

Low-protein Diets

Do not offer low-protein diets (dietary protein intake less than 0.6–0.8 g/kg/day) to people with CKD. [new 2014]

Self-management

Ensure that systems are in place to:

- Inform people with CKD of their diagnosis
- Enable people with CKD to share in decision-making about their care
- Support self-management (this includes providing information about blood pressure, smoking cessation, exercise, diet and medicines) and enable people to make informed choices. [new 2014]

Give people access to their medical data (including diagnosis, comorbidities, test results, treatments and correspondence) through information systems, such as Renal PatientView [   ], to encourage and help them to self-manage their CKD. [new 2014]

Referral Criteria

Take into account the individual's wishes and comorbidities when considering referral. [2008]

People with CKD in the following groups should normally be referred for specialist assessment:

- GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- ACR 30 mg/mmol or more (ACR category A3), together with haematuria
- Sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months
- Hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also the NGC summary of the NICE guideline Hypertension. Clinical management of primary hypertension in adults [NICE clinical guideline 127])
- Known or suspected rare or genetic causes of CKD
- Suspected renal artery stenosis. [2008, amended 2014]

Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist. [2008]

Once a referral has been made and a plan jointly agreed (between the person with CKD or their carer and the healthcare professional), it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral

or re-referral should be specified. [2008]

People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload. [2008]

Pharmacotherapy

Blood Pressure Control

In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg†. [2008]

In people with CKD and diabetes, and also in people with an ACR of 70 mg/mmol or more, aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg†. [2008]

†The Guideline Development Group (GDG) searched for and appraised evidence on blood pressure control, and did not set out to establish definitive safe ranges of blood pressure in CKD. The evidence presented in the full version of the original guideline document does not therefore include safety of low blood pressure, but some such evidence does exist. The GDG set out a range of blood pressure targets, given in these recommendations, which in their clinical experience will inform good practice in CKD.

Choice of Antihypertensive Agent

Offer a low-cost renin–angiotensin system antagonist to people with CKD and:

- Diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)
- Hypertension and an ACR of 30 mg/mmol or more (ACR category A3)
- An ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease)‡. [new 2014]

‡Note: The evidence to support these criteria is limited in people aged over 70 years.

Do not offer a combination of renin–angiotensin system antagonists to people with CKD. [new 2014]

Follow the treatment recommendations in the NGC summary of the NICE guideline Hypertension. Clinical management of primary hypertension in adults (NICE clinical guideline 127) for people with CKD, hypertension and an ACR of less than 30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes. [new 2014]

To improve concordance, inform people who are prescribed renin–angiotensin system antagonists about the importance of:

- Achieving the optimal tolerated dose of renin–angiotensin system antagonists and
- Monitoring eGFR and serum potassium in achieving this safely. [2008]

In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008]

Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre. [2008, amended 2014]

When hyperkalaemia precludes use of renin–angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked. [2008]

Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin–angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required. [2008]

Stop renin–angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued. [2008]

Following the introduction or dose increase of renin–angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%. [2008]

If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin–angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin–angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%. [2008]

If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:

- Investigate other causes of a deterioration in renal function, such as volume depletion or concurrent medication (for example, NSAIDs)
- If no other cause for the deterioration in renal function is found, stop the renin–angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required. [2008]

Statins

Follow the recommendations in the NGC summary of the NICE guideline Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (NICE clinical guideline 181) for the use of statins in CKD. [new 2014]

Oral Antiplatelets and Anticoagulants

Offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. [new 2014]

Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- Prior stroke or transient ischaemic attack
- Age 75 years or older
- Hypertension
- Diabetes mellitus
- Symptomatic heart failure. [new 2014]

Other Complications

Bone Metabolism and Osteoporosis

Do not routinely measure calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3). [2008]

Measure serum calcium, phosphate and PTH concentrations in people with a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists, seek specialist opinion. [2008]

Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3). [2008]

Vitamin D Supplements in the Management of CKD–Mineral and Bone Disorders

Detailed advice on the management of CKD–mineral and bone disorders is beyond the scope of this guideline. If uncertain, seek advice from a local renal service.

Do not routinely offer vitamin D supplementation to manage or prevent CKD–mineral and bone disorders. [new 2014]

Offer cholecalciferol or ergocalciferol to treat vitamin D deficiency in people with CKD and vitamin D deficiency. [new 2014]

If vitamin D deficiency has been corrected and symptoms of CKD–mineral and bone disorders persist, offer alfacalcidol (1-alpha-hydroxycholecalciferol) or calcitriol (1-25-dihydroxycholecalciferol) to people with a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5). [new 2014]

Monitor serum calcium and phosphate concentrations in people receiving alfacalcidol or calcitriol supplements. [2014]

Anaemia

If not already measured, check the haemoglobin level in people with a GFR of less than 45 ml/min/1.73 m^2 (GFR category G3b, G4 or G5) to identify anaemia (haemoglobin less than 110 g/litre [11.0 g/dl], see the NGC summary of the NICE guideline Anaemia management in people with chronic kidney disease [NICE clinical guideline 114]). Determine the subsequent frequency of testing by the measured value and the clinical

circumstances. [2008]

Oral Bicarbonate Supplements in the Management of Metabolic Acidosis

Detailed advice on the management of metabolic acidosis is beyond the scope of this guideline. If uncertain, seek advice from a local renal service.

Consider oral sodium bicarbonate supplementation for people with both:

- A GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5) and
- A serum bicarbonate concentration of less than 20 mmol/litre. [new 2014]

Definitions:

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Note: The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2008]. In particular, for recommendations labelled [2008] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Clinical Algorithm(s)

An algorithm titled "Algorithm A" is provided in the full version of the original guideline document (see the "Availability of Companion Documents" field).

In addition, a National Institute for Health and Care Excellence (NICE) care pathway titled "Chronic Kidney Disease Overview" is available from the NICE Web site ☐.

Scope

Disease/Condition(s)

Chronic kidney disease (CKD)

Other Disease/Condition(s) Addressed

- Anaemia
- Diabetes
- Heart failure
- Hypertension
- Osteoporosis
- Stroke

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Cardiology

Endocrinology

Family Practice

Geriatrics

Internal Medicine

Nephrology

Nutrition

Urology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Patients

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To update the 2008 guidance on the care of adults with chronic kidney disease (CKD) in areas where new data have become available and to provide new guidance in areas where previously no evidence existed, including:

- Identification and investigation of people who have or are at risk of developing CKD
- Classification of CKD and identification of those at risk of complications and progression of CKD
- The definition of progression of CKD
- The relationship between acute kidney injury and CKD
- Self-management in CKD
- Pharmacotherapy in CKD

Target Population

Adults aged 18 and over who have or are at risk of developing chronic kidney disease (CKD), with specific consideration given to the needs of subgroups:

- Older people (75 years and older)
- Black and minority ethnic people where these differ from the needs of the general population
- People at high risk of developing CKD (for example, people with: diabetes, hypertension, cardiovascular disease, or people recovering from acute kidney injury)

Note: The guideline does not cover:

Children and young people (aged under 18 years)
People receiving renal replacement therapy (RRT)
People with acute kidney injury (acute renal failure) and rapidly progressive glomerulonephritis
Pregnant women

Interventions and Practices Considered

Diagnosis/Evaluation/Risk Assessment

1. Creatinine-based estimate of glomerular filtration rate (eGFRcreatinine)
2. Cystatin C-based estimate of glomerular filtration rate (eGFRcystatinC)
3. Reporting and interpreting glomerular filtration rate (GFR) values
4. Detection of protein in the urine using urine albumin/creatinine ratio (ACR) (preferred) or protein/creatinine ratio (PCR)
5. Detection of blood in the urine using reagent strips
6. Offering testing for chronic kidney disease (CKD) based on presence of risk factors
7. Classification of CKD
8. Investigating the cause of CKD and determining risk of adverse outcome
9. Renal ultrasound in selected patients with CKD
10. Frequency of monitoring (eGFRcreatinine and ACR)
11. Risk assessment for CKD progression
12. Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with a GFR of less than 30 ml/min/1.73 m^2
13. Checking haemoglobin level to identify anaemia

Management/Treatment/Prevention

1. Patient education about the stages and causes of CKD, the associated complications, and the risk of progression
2. Specialist referral
3. Lifestyle advice
4. Dietary interventions (advice on potassium, phosphate, calorie, salt intake)
5. Low-protein diet (not recommended)
6. Support for self-management

7. Pharmacotherapy
   - Blood pressure control (angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs])
   - Statins
   - Antiplatelet and anticoagulant drugs
   - Bisphosphonates for prevention/treatment of osteoporosis
   - Vitamin D (cholecalciferol, ergocalciferol, alfacalcidol, calcitriol) in the management of CKD–mineral and bone disorders
   - Oral bicarbonate supplements in the management of metabolic acidosis

Major Outcomes Considered

- Clinical effectiveness
  - Sensitivity, specificity, and accuracy of diagnostic tests
  - Mortality (all cause and cardiovascular)
  - Hospitalisation
  - Cardiovascular disease
  - Chronic kidney disease (CKD) progression: change in estimated glomerular filtration rate (eGFR), occurrence of end-stage renal disease (ESRD)
  - Complications of CKD
  - Patient safety (serious adverse events such as major bleeding)
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, and with a framework of population, index tests, comparator test, reference standard and statistical measures for reviews of diagnostic test accuracy. For review questions about prognostic factors the framework used was population, presence of prognostic factor, absence of factor and statistical measures. This was to guide the literature searching process and to facilitate the development of recommendations by the Guideline Development Group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full version of the original guideline document).

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per The Guidelines Manual (2012) (see the "Availability of Companion Documents" field). Clinical databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where

possible, searches were restricted to articles published in English language. All searches were conducted on the following core databases, MEDLINE, EMBASE, CINAHL and The Cochrane Library. All searches were updated on 25 November 2013. No papers after this date were considered.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking the GDG for known studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F in the full version of the original guideline document.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearinghouse (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (www.consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to chronic kidney disease (CKD) in the National Health Service (NHS) economic evaluation database (NHS EED), the Health Economic Evaluations Database (HEED) and health technology assessment (HTA) databases with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE, with a specific economic filter, from 2009, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix F in the full version of the original guideline document. All searches were updated on 25 November 2013. No papers published after this date were considered.

Evidence of Effectiveness

The Research Fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C in the full version of the original guideline document).

Inclusion/Exclusion

See the review protocols in Appendix C in the full version of the original guideline document for full details.

The following population groups were excluded in all reviews:

- People receiving renal replacement therapy
- People with acute kidney injury and rapidly progressive glomerulonephritis
- Children and young people under 18 years
- Pregnant women

Evidence of Cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The Health Economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies.

Inclusion/Exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially applicable as economic evidence.

Studies were excluded if they:

- Reported cost per hospital (not per patient), or
- Reported average (not incremental) cost effectiveness without disaggregated costs and effects
- Were abstracts, posters, reviews, letters/editorials, foreign language publications or unpublished studies
- Were judged to have an applicability rating of 'not applicable' (this included studies that took the perspective of a non-Organisation for Economic Co-operation and Development [OECD] country).

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (The Guidelines Manual, Appendix G [see the "Availability of Companion Documents" field] and the health economics research protocol in Appendix C in the full version of the original guideline document).

When no relevant economic analysis was found from the economic literature review, relevant United Kingdom (UK) National Health Service (NHS) unit costs related to the compared interventions were presented to the GDG to inform the their decisions. The unit costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have changed slightly by the time of publication.

Number of Source Documents

Refer to Appendix D in the full version of the original guideline document (see the "Availability of Companion Documents" field) for flow diagrams of clinical selection, which detail the total number of studies included for each guideline topic.

Refer to Appendix E in the full version of the original guideline document (see the "Availability of Companion Documents" field) for a flow diagram of economic article selection for the guideline.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very	Any estimate of effect is very uncertain.

Low Level	Description

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The information below refers to the methods used for evidence review of 2014 guideline recommendations. Methods used for 2008 recommendations are detailed in section 3.2 of the full version of the original guideline document.

Evidence of Effectiveness

The Research Fellow:

- Critically appraised relevant studies using the appropriate checklist as specified in The Guidelines Manual (see the "Availability of Companion Documents" field).
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G of the full version of the original guideline document).
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups):
  - Randomised studies: meta-analysed, where appropriate and reported in Grading of Recommendations Assessment, Development, and Evaluation (GRADE) profiles (for clinical studies) – see the full version of the original guideline document for details
  - Diagnostic and prognostic studies: data presented as a range of values in adapted GRADE profiles
  - Qualitative studies: each study summarised in a table where possible, otherwise presented in a narrative.

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes: all-cause and cardiovascular mortality, chronic kidney disease (CKD) progression (occurrence of end stage renal disease [ESRD]), acute kidney injury (AKI), cardiovascular events, hospitalisation, incident CKD, adherence, major bleeding, minor bleeding, fracture and hypercalcaemia. The continuous outcomes CKD progression (change in estimated glomerular filtration rate [eGFR]), health related quality of life and nutritional status (measured by subjective global assessment or change in body mass index [BMI]) were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. For cases where there are no events in either arm, the Peto odds ratio will be calculated instead of the risk ratio as it has been shown to be the least biased and most powerful method of determining effect size for rare events.

Where available, hazard ratios were presented for time-to-event data (e.g., mortality, progression of CKD, occurrence of cardiovascular events). Time-to-event data should not be analysed as the continuous outcome, mean time-to-event (or mean duration of remission) with its standard deviation, because the relevant times are only known for the subset of participants who have had the event. Censored participants who have not had the event are either treated as uncensored - which will underestimate the time to event (bias) – or are excluded, which will again introduce bias, particularly if the censored times are longer than the uncensored times. Survival rates at different time points (treating as dichotomous outcomes) can also lead to bias because of failure to take account of censoring. Dichotomising of time-to-event data is only acceptable when all the participants have been followed up to the particular time point. There is a risk of bias that individual studies may select time points for reporting that maximise the difference between interventions.

The most appropriate way of summarising time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard

ratio. Hazard is similar in notion to risk, but is subtly different in that it measures instantaneous risk and may change with time. A hazard ratio is interpreted in a similar way to a risk ratio, because it describes how many times more (or less) likely a participant is to suffer the event at a particular point in time if they receive the experimental rather than the control intervention.

Where studies reported stage of CKD or degree of proteinuria these were considered in the data synthesis.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of $>50\%$ to indicate significant heterogeneity. Where significant heterogeneity was present, redefined subgroup analyses were carried out for: age, black and minority ethnic groups, diabetes, hypertension, and cardiovascular disease. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow up was also taken into consideration prior to including in a sensitivity analysis.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p-values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software. Where p values were reported as "less than", a conservative approach was undertaken. For example, if p value was reported as "p ≤0.001", the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Individual Patient Data (IPD) Meta-Analysis

IPD meta-analysis is a specific type of systematic review. Instead of extracting summary data from study reports, the original data for each participant in an included study are sought directly from the researchers responsible for that study. IPD meta-analyses are regarded as gold standard reviews, surpassing systematic reviews of summary data. They are often carried out for time-to-event outcomes, which are themselves analysed by following the course of individual patients over time.

Advantages of IPD meta-analyses are:

- Data from unpublished studies can be included.
- They allow time-to-event analyses and facilitate analysis of studies with long term follow up.
- Data checking is enabled.
- Some aspects of risk of bias are reduced: outcome reporting bias and reasons for missing outcome data can be identified; problems with reporting of risk of bias are largely removed.
- Data can be re-analysed in a consistent way (e.g., reviewers can carry out analyses according to intention-to-treat principles, even if the original trial analyses did not do this).
- Subgroup analyses using IPD are much more straightforward than in conventional aggregate data meta-analyses.

In the latter, it is usually very difficult to extract sufficient compatible data to undertake meaningful subgroup analyses (e.g., data are reported as study level characteristics, such as mean age), and it is especially difficult to characterise individuals by more than one factor at a time. In contrast, IPD permit straightforward categorisation of individuals for subgroup analysis (stratified by study) defined by single or multiple factors.

Analysis is usually carried out in two stages: Each individual study is analysed in the same way, as set out in the meta-analysis protocol or analysis plan. Then summary statistics of each study analysis are combined to provide a pooled estimate of effect in the same way as for a conventional systematic review. This approach maintains the randomisation within individual trials. Combining the patients from all trials into one large cohort first destroys randomisation and is unacceptable. However, regression analysis with trial number as one of the variables is acceptable.

Where IPD studies were identified for a review question, they were included in preference of individual studies (chapters 6.1 and 6.3 in the full version of the guideline for classification of CKD and cause of CKD respectively).

Data Synthesis for Prognostic Factor Reviews

Odds ratio, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers, and standard errors were calculated from the 95% confidence intervals. The log of the effect size with its standard error was entered into the generic inverse variance technique in the Cochrane Review Manager (RevMan5.1) software. Studies were not combined in a meta-analysis for observational studies. Sensitivity analyses were carried out on the basis of study quality and results were reported as ranges.

Data Synthesis for Diagnostic Test Accuracy Review

Diagnostic test accuracy was considered in the chapter on the measurement of kidney function (chapter 5.1 in the full version of the original guideline document). The critical outcomes in the review are those used widely in the literature to compare GFR estimating equations: accuracy, bias and precision. Bias describes the difference between estimates of GFR and the measured GFR. This is commonly described as the mean or median bias. Precision is the variability of the estimate of GFR compared to the measured value. The root mean square error (RMSE) of the regression of estimated GFR versus measured GFR is considered to be a direct measure of precision. However, overall interquartile range (IQR) for the differences between estimated GFR and measured GFR, an indirect measure of precision, was more widely reported by studies and so was used in the analysis.

Accuracy is affected by both bias and precision. Accuracy is represented by the P30: the percentage of estimated GFR values lying within 30% of the measured GFR.

The following outcomes were also considered as they are more standard measures of diagnostic accuracy but are less frequently reported in the CKD literature: sensitivity, specificity, and area under the curve. Net reclassification index, a statistic that measures the improvement in prediction performance was also considered important, however it is usually used in the literature to analyse the reclassification between eGFR categories in population studies where only estimated values of GFR (and not measured values) are available.

Data Synthesis for Qualitative Reviews

A qualitative review was considered in the chapter on self-management (chapter 8.6 in the full version of the original guideline document). A customised quality assessment for qualitative studies was undertaken and a narrative summary of the findings is presented.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included RCT and observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The summary of findings was presented as two separate tables in this guideline. The "Clinical/Economic Study Characteristics" table includes details of the quality assessment while the "Clinical/Economic Summary of Findings" table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of patients with an adverse event, the event rates (n/N: number of patients with events divided by sum of number of patients) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the Clinical Study Characteristics table if it was apparent.

Each outcome was examined separately for the quality elements listed and defined in Table 3 in the full version of the original guideline document and each graded using the quality levels listed in Table 4 in the full version of the original guideline document. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome.

The GRADE toolbox is currently designed only for randomised trials and observational studies but the quality assessment elements and outcome presentation for diagnostic accuracy and prognostic reviews were adapted.

Grading the Quality of Clinical Evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision and reporting bias. These criteria are detailed in the full version of the guideline. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results

showed no effect. Each quality element considered to have "serious" or "very serious" risk of bias were rated down -1 or -2 points respectively.

3. The downgraded/upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW or VERY LOW if 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes.

Study Limitations

The main limitations for randomised controlled trials are listed in Table 6 in the full version of the original guideline document.

See sections 3.1.4.6 to 3.1.4.9 in the full version of the original guideline document for information on inconsistency, indirectness, imprecision, and risk of bias.

Evidence of Cost-effectiveness

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the economic literature
- Undertook new cost-effectiveness analysis in priority areas

Literature Review

The Health Economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in The Guidelines Manual Appendix G (see the "Availability of Companion Documents" field).
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix H in the full version of the original guideline document).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter write-ups in the full version of the original guideline document).

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The Guidelines Manual, Appendix G (see the "Availability of Companion Documents" field). It also shows incremental costs, incremental outcomes (for example, quality-adjusted life years [QALYs]) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis. See Table 8 in the full version of the original guideline document for more details.

If a non-United Kingdom (UK) study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): The guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

The Guideline Development Group

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline. The group met every 4-6 weeks during the development of the guideline.

Developing Recommendations

Over the course of the guideline development process, the Guideline Development Group (GDG) was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendix G and H in the full version of the original guideline document (see the "Availability of Companion Documents" field)
- Summary of clinical and economic evidence and quality (as presented in individual chapters in the full version of the original guideline document)
- Forest plots and summary receiver operated characteristic (ROC) curves (Appendix I in the full version of the original guideline document)
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendices L and M in the full version of the original guideline document)

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs. When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus based recommendations include the balance between potential harms and benefits, economic or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were done through discussions in the GDG. The GDG may also consider whether the uncertainty is sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see section 3.1.6.1 in the full version of the original guideline document).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally the GDG uses 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Note: The National Institute for Health and Care Excellence (NICE) began using this approach to denote the strength of recommendations in

guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending [2008]. In particular, for recommendations labelled [2008] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Cost Analysis

Relevant health economic evidence for recommendations can be found in the specific chapters of the full version of the original guideline document.

See Appendices L and M in the full version of the original guideline document for details of the health economic analyses undertaken for this guideline update.

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the Health Economist in priority areas. Priority areas for new health economic analyses were agreed by the Guideline Development Group (GDG) after formation of the review questions and consideration of the available health economic evidence.

Additional data for the analysis was identified as required through additional literature searches undertaken by the Health Economist, and discussion with the GDG. Model structure, inputs and assumptions were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

See Appendices L and M in the full version of the original guideline document for details of the health economic analyses undertaken for this guideline update.

Cost-effectiveness Criteria

The National Institute for Health and Care Excellence (NICE) report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.

In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with all other strategies.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the 'Social value judgements: principles for the development of NICE guidance'.

When QALYs are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guidance is subject to a six week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the National Institute for Health and Care Excellence (NICE) website.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Potential benefits of vitamin D therapy in people with chronic kidney disease (CKD) include increased bone mineral density and muscle strength, reduced risk of falls and fractures, and reduction in hyperparathyroidism.
- Appropriate management of individuals with or at risk of CKD

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for benefits of specific interventions.

Potential Harms

- A balance must be struck between ensuring that people receive optimal therapy with angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blockers (ARBs) but do not suffer adverse effects from using these drugs. The two main concerns about using ACE inhibitor/ARBs are the development of hyperkalaemia and worsening of underlying kidney function, usually as a result of their use in people with undiagnosed renovascular disease.
- All people who have indications for ACE inhibitors or ARBs are at higher risk of acute kidney injury (AKI); therefore, these drugs should be temporarily stopped during an acute illness that increases the risk of AKI (for example, diarrhoea, vomiting and other conditions leading to dehydration or shock).
- Clinicians should be aware of the increased risk of bleeding in people with chronic kidney disease (CKD) given antiplatelet drugs.
- Potential adverse effects of vitamin D therapy are hypercalcaemia and extraskeletal (vascular) calcification, and increased cardiovascular risk.
- False negative and false positive results of diagnostic tests

Refer to the "Trade off between clinical benefits and harms" sections in the full version of the original guideline document (see the "Availability of Companion Documents" field) for harms of specific interventions.

Contraindications

Contraindications

- Anaphylaxis and angioedema are absolute contraindications to angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) therapy, and symptomatic hypotension and severe aortic stenosis may also preclude their use.
- Changes in glomerular filtration rate (GFR) and potassium during treatment with ACE inhibitor/ARBs may be significantly influenced by a person's volume status, degree of sodium depletion, and concurrent medications. Many people 'intolerant' of ACE inhibitor/ARB treatment may be successfully treated once these factors have been addressed. Educating the healthcare community about these relative contraindications, and clearly stating what parameters should be monitored, how often these parameters should be monitored, and what levels are acceptable, could significantly affect outcomes in many people who might otherwise not be treated with ACE inhibitor/ARBs (and also help avoid unwanted complications).

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer and informed by the summary of product characteristics of any drugs they are considering.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- Patients and healthcare professionals have rights and responsibilities as set out in the National Health Service (NHS) Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.
- NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

Implementation of the Guideline

Description of Implementation Strategy

Implementation tools and resources to help clinicians put the guideline into practice are also available on the National Institute for Health and Care Excellence (NICE) Web site (see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Investigations for Chronic Kidney Disease (CKD)

- Clinical laboratories should:
  - Use the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to estimate creatinine-based glomerular filtration rate (eGFRcreatinine), using creatinine assays with calibration traceable to standardised reference material.
  - Use creatinine assays that are specific (for example, enzymatic assays) and zero-biased compared with isotope dilution mass spectrometry (IDMS).
  - Participate in a UK national external quality assessment scheme for creatinine. [new 2014]
- Consider using cystatin C-based estimate of glomerular filtration rate (eGFRcystatinC) at initial diagnosis to confirm or rule out CKD in people with:
  - An eGFRcreatinine of 45–59 ml/min/1.73 m^2, sustained for at least 90 days and
  - No proteinuria (albumin:creatinine ratio [ACR] less than 3 mg/mmol) or other marker of kidney disease. [new 2014]
- Do not diagnose CKD in people with:
  - An eGFRcreatinine of 45–59 ml/min/1.73 m^2 and
  - An eGFRcystatinC of more than 60 ml/min/1.73 m^2 and
  - No other marker of kidney disease. [new 2014]
- Offer testing for CKD using eGFRcreatinine and ACR to people with any of the following risk factors:

- Diabetes
- Hypertension
- Acute kidney injury (AKI)
- Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- Structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- Multisystem diseases with potential kidney involvement – for example, systemic lupus erythematosus
- Family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease
- Opportunistic detection of haematuria. [new 2014]

Classification of Chronic Kidney Disease

- Classify CKD using a combination of GFR and ACR categories (as described in table 1 in the original guideline document). Be aware that:
  - Increased ACR is associated with increased risk of adverse outcomes.
  - Decreased GFR is associated with increased risk of adverse outcomes.
  - Increased ACR and decreased GFR in combination multiply the risk of adverse outcomes. [new 2014]

Frequency of Monitoring

- Use table 2 in the original guideline document to guide the frequency of GFR monitoring for people with, or at risk of, CKD, but tailor it to the person according to:
  - The underlying cause of CKD
  - Past patterns of eGFR and ACR (but be aware that CKD progression is often nonlinear)
  - Comorbidities, especially heart failure
  - Changes to their treatment (such as renin–angiotensin–aldosterone system [RAAS] antagonists, NSAIDs and diuretics)
  - Intercurrent illness
  - Whether they have chosen conservative management of CKD. [new 2014]

Implementation Tools

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

Staff Training/Competency Material

> For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 59 p. (Clinical guideline; no. 182).

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest, which were also recorded (Appendix B in the full version of the original guideline document [see the "Availability of Companion Documents" field]).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Chronic Conditions. Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 Sep. 36 p. (Clinical guideline; no. 73).

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site [   ].

Availability of Companion Documents

The following are available:

- Chronic kidney disease (partial update). Early identification and management of chronic kidney disease in adults in primary and secondary care. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 447 p. (Clinical guideline; no. 182). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site [   ].
- Chronic kidney disease (partial update). Early identification and management of chronic kidney disease in adults in primary and secondary care. Guideline appendices A-R. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 1023 p. (Clinical guideline; no. 182) Electronic copies: Available from the NICE Web site [   ].
- Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. Costing statement. London (UK): National Institute for Health and Care Excellence; 2014 Jul. 8 p. (Clinical guideline; no. 182). Electronic copies: Available from the NICE Web site [   ].
- Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence; 2014 Jul. (Clinical guideline; no. 182). Electronic copies: Available from the NICE Web site [   ].
- Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. Online learning tool. Available from the BMJ Web site [   ].
- The guidelines manual 2012. London (UK): National Institute for Health and Care Excellence (NICE); 2012 Nov. Electronic copies: Available from the NICE Web site [   ].

Patient Resources

The following is available:

- Identifying and treating chronic kidney disease (CKD). Information for the public. London (UK): National Institute for Health and Care Excellence; 2014 Jul. 14 p. (Clinical guideline; no. 182). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site [   ]. Also available for download as a Kindle or EPUB ebook from the NICE Web site [   ].

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This summary was completed by ECRI Institute on October 2, 2009. This summary was updated by ECRI Institute on December 10, 2010 following the U.S. Food and Drug Administration (FDA) advisory on Bisphosphonates. This summary was updated by ECRI Institute on June 27, 2011 following the U.S. Food and Drug Administration advisory on Zocor (simvastatin). This summary was updated by ECRI Institute on October 12, 2011 following the U.S. Food and Drug Administration (FDA) advisory on Reclast (zoledronic acid). This summary was updated by ECRI Institute on April 13, 2012 following the U.S. Food and Drug Administration advisories on Statin Drugs and Statins and HIV or Hepatitis C drugs. This summary was updated by ECRI Institute on October 31, 2014.

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